Further, lipid lowering may not be as beneficial in advanced disease. We compared survival associated with statin therapy in CAD pts with and without LVD.

Methods: A cohort of 2,202 non-LVD pts and 364 LVD pts with angiographically defined CAD (≥70% stenosis), were studied from the registry of the Intermountain Heart Collaborative Study at LDS Hospital. Risk factors and clinical data, including statin prescription at discharge, were recorded at baseline. Pts were followed for 3.0±1.9 years (maximum 7.7 years) to determine the incidence of mortality. Cox regression and Kaplan-Meier estimates were used to model survival in both groups.

Results: Patient age (63±12 years) and gender (34% female) did not differ between the groups. Statins were prescribed at discharge for 28% of non-LVD and 26% of LVD pts (p=NS). Among non-LVD patients, mortality was 6.8% for statin prescribed pts and 12.7% for those not prescribed statins (p=0.005 by log-rank); among LVD pts, mortality was 16.0% when prescribed statins and 32.6% when no statin was prescribed (p=0.017 by log-rank). After adjustment for covariables, these associations remained for non-LVD pts (hazard ratio [HR]= 0.66, 95% CI= 0.47-0.93), and LVD pts (HR=0.57, CI= 0.33-0.99). No interaction was found between statin prescription and EF for mortality (p-interaction=0.71).

Conclusion: Proportionate benefit from statin prescription was similar in LVD and non-LVD groups, but absolute benefit was greater in LVD pts (16% vs. 6% absolute mortality reduction). These results demonstrate the benefit of statin discharge prescription, regardless of degree of LVD and emphasize current underutilization, particularly in those with LVD.

1184-77 Utilization of ACE-I and β-blocker Therapy in Managed Care Patients With Heart Failure: NC ACE Project

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Background: Heart failure (HF) results in substantial morbidity and mortality in the US. Despite evidence-based guidelines recommending proven therapies, translation into clinical practice is suboptimal. The goal of the North Carolina Achieving Cardiac Excellence (NC ACE) Project is to increase the utilization of angiotensin converting enzyme inhibitor (ACE-I) and β-blocker therapies in patients with HF. The purpose of this study is to compare the management of Medicare and Medicaid patients with HF enrolled in managed care.

Methods: Data were abstracted from outpatient medical records for 971 Medicare (3 managed care plans) and 654 Medicaid (2 plans) patients treated for HF during 2000. Patients receiving dialysis were excluded.

Results: Compared to Medicaid patients, Medicare patients were older (76±9 vs. 59±14 years), more likely to be white (84 vs. 47%), and men (50 vs. 30%). More than 80% of Medicare (n=795) and Medicaid (n=526) patients had documentation of a quantitative or qualitative assessment of left ventricular function (LVF). Left ventricular systolic dysfunction (LVSD) was present in 37% (n=297) of Medicare patients and 37% (n=197) of Medicaid patients.

Indicator	Medicare	Medicaid
LVF Assessment	849 (87%)	573 (89%)
ACE-I in LVSD	215 (72%)	147 (75%)
ACE-I Intolerance	42 (14%)	23 (12%)
β-blocker in LVSD	144 (48%)	96 (49%)
β-blocker Intolerance	34 (12%)	25 (13%)

Conclusion: Assessment and treatment of HF appears similar in Medicare and Medicaid managed care patients. Although not optimal, these rates are substantially higher than previously reported. Opportunities for increasing appropriate use of β-blockers should be prioritized in these populations.

1184-78 Hemodynamic Effects of Levosimendan in Addition to Dobutamine Infusion in Patients With Advanced Heart Failure Intractable to Dobutamine Infusion Alone

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Background: Levosimendan is a new calcium-sensitizing agent with positive inotropic and vasodilatory effects.

Purpose: This study measured the magnitude and duration of the hemodynamic response to an infusion of levosimendan in clinically unstable patients with advanced congestive heart failure (CHF) pretreated with dobutamine and furosemide.

Methods: In thirteen patients with advanced CHF, 48-77 years of age, in NYHA functional class IV, previously treated with intermittent dobutamine infusions, and hospitalized for clinical instability despite continuous dobutamine, 10 μg/kg/min, and furosemide, 10 mg/h, infusions, a continuous infusion of levosimendan, in a bolus of 6 μg/kg, followed by a 0.2 μg/kg/min infusion for 24 h, was added. The patients were followed for 7 days, including serial right-heart catheterizations. The effect on Systolic Blood Pressure (SBP), Cardiac Index (CI), Pulmonary Capillary Wedge Pressure (PCWP), Right Atrial Pressure (RA) and Systemic Vascular Resistance (SVR), before and at 12 hours, 24 hours and 1 week after levosimendan administration, was recorded.

Results: The results are summarized in the Table

	before	12h	24h	1week
SBP (mmHg)	92±13	96±12*	95±16	96±14
CI (l/min/m^2)	1.7±0.3	2.4±0.4*	2.5±0.6*	2.5±0.8*
PCWP (mmHg)	28±6	25±6*	23±8*	22±10*
RA (mmHg)	15±6	11±5*	10±6*	10±6*
SVR (IU Wood)	19±7	14±5*	14±4*	14±5*

*p<0.05 versus baseline

Conclusion: The addition of levosimendan had a sustained therapeutic effect in clinically unstable patients with CHF refractory to continuous dobutamine and furosemide infusions. This regimen could be used as a bridge to left ventricular assist device implantation or heart transplantation.

1184-79 Acute Intravenous Ranolazine Improves Left Ventricular Function in Dogs With Heart Failure: A Dose Escalation Study

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Background: To explore the use of intravenous (iv) ranolazine, a partial fatty acid oxidation inhibitor, as acute therapy for heart failure (HF), we determined the effects of up-titration and reversibility of ranolazine in 8 dogs with microembolizations-induced HF. **Methods:** Ranolazine was given as 0.05 mg/kg bolus followed by iv infusion at 0.1, 0.3, 1.0 and 3.0 mg/kg/hr each for 1 hour. Heart rate (HR), peak left ventricular (LV) systolic pressure (LVSP), stroke volume (SV), LV end-diastolic volume (EDV), LV end-systolic volume (ESV), LV ejection fraction (EF) and ranolazine plasma concentration (RANc) were measured at baseline and at the end of each dose. **Results:** The results are shown in the table. Ranolazine decreased ESV without affecting EDV, thus increasing EF at all doses in a dose and RANc dependent manner. The increase in EF plateaued at doses ≥0.3 mg/kg/hr, suggesting a half maximal response at ~0.1 mg/kg/hr at RANc of 67±11 ng/ml. Ranolazine had nominal effects to reduce HR at doses >0.3 mg/kg/hr and LVSP at a dose of 3.0 mg/kg/hr. The effect of ranolazine (0.05 mg/kg bolus + 0.3 mg/kg/hr for 1 hr) declined after stopping infusion in proportion to RANc. **Conclusions:** Intravenous ranolazine improves LV function in dogs with chronic HF in a reversible, dose and concentration dependent manner with little or no impact on HR and LVSP.

	RanolazineDose (mg/kg/hr)				
	Baseline	0.1	0.3	1.0	3.0
HR (beats/min)	83 ± 4	80 ± 6	75 ± 5*	74 ± 5*	73 ± 5*^
LVSP (mmHg)	96 ± 3	102 ± 4	97 ± 3	94 ± 3	89 ± 4*^
SV (ml)	19 ± 1	23 ± 1*	25 ± 1*^	26 ± 1*^	26 ± 1*^
EDV (ml)	66 ± 4	66 ± 3	65 ± 4	66 ± 3	65 ± 4
ESV (ml)	47 ± 4	43 ± 4*	41 ± 3*^	39 ± 3*^	39 ± 3*^
EF (%)	30 ± 2	36 ± 2*	38 ± 2*^	39 ± 3*^	39 ± 3*^
RANc (ng/ml)	0	67 ± 4	106 ± 94	557 ± 87	1259 ± 1354

*=P<0.05 vs. Baseline; ^=P<0.05vs. 0.1 mg/kg/hr

1184-80 Effect of the Angiotensin Converting Enzyme Inhibitor Trandolapril on Functional Status and Furosemide Consumption in Patients With Reduced Left Ventricular Function After Myocardial Infarction

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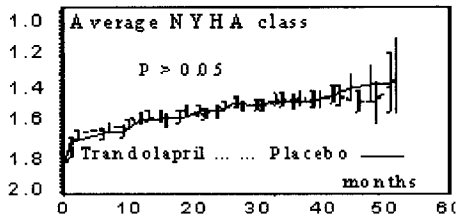
Background: Information on the direct benefit of angiotensin converting enzyme inhibitors on symptoms are scarce and in contrast to the overwhelming amount of information on survival. Effect of the use of concommitant diuretic therapy on symptoms has been also questioned. Therefore we studied development of New York Heart Association (NYHA) classification and use of furosemide in the Trandolapril Cardiac Evaluation Study (TRACE).

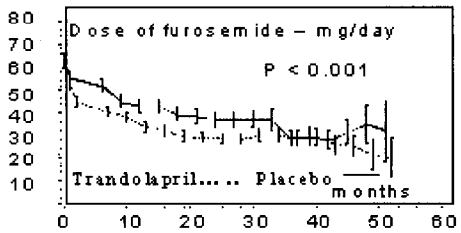
Methods: In TRACE 1749 consecutive patients with left ventricular systolic dysfunction after myocardial infarction (MI) were randomized to either placebo or trandolapril. The patients were assessed for changes in NYHA classes and use of furosemide every 3 months and were followed up 2-4 years.

Results: There were no differences in baseline characteristics between the two treatment groups. The majority of the patients were in NYHA classes II and I. Both placebo and trandolapril groups showed equal improvement in NYHA classes without any significant differences (P> 0.05, figure). This result was also found in patients with NYHA class II or greater at the time of randomization. Trandolapril resulted in a mild but significant reduction of the use of furosemide with a mean reduction of 12 mg/day overall during follow up (p<0.001, figure).

Conclusion: Despite a significant reduction in mortality, trandolapril did not improve

NYHA classes in patients with left ventricular dysfunction after MI. Trandolapril resulted in significantly lower furosemide consumption.





1184-81 **Elevated Plasma Xanthine Oxidase Activity in Chronic Heart Failure: Source of Increased Oxygen Radical Load and Effect of Allopurinol in a Placebo Controlled, Double Blinded Treatment Study**

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Background: Elevated xanthine oxidase (XO) activity contributes to production of reactive oxygen species. Hyperuricemia is common in chronic heart failure (CHF), however, enzyme activity of circulating plasma XO has not been studied in CHF. We hypothesised, that plasma XO activity is elevated in CHF compared to healthy controls, paralleled by increased free radical load, and that XO inhibition with allopurinol decreased both. As a marker of free radical load serum allantoin was measured, which is generated in the humans exclusively via non-enzymatic oxygen radical dependent urate oxidation.
Methods: In 67 CHF patients (mean age 65±10y, NYHA 2.4±0.7, peak VO_2 18.6±6.8 mL/kg/min) and 15 controls (age 33±10y) we measured plasma XO activity (HPLC), uric acid (UA), and allantoin (gas chromatography-mass spectrometry). In 17 CHF patients with known hyperuricemia (UA 517±95µmol/L), the effect of allopurinol (300mg od for 1 week) was tested in a placebo controlled double-blinded, cross-over study.
Results: CHF patients were hyperuricemic (UA 481±143µmol/L; normal range 210-440 µmol/L) and had increased plasma XO activity (7.01±0.60 vs 0.89±1.23 vs µU/ml; p<0.001). The upper limit of normal was defined as 3.35 µU/ml XO (normal mean value +2SD). All but one control and 11 patients (16%) had normal plasma XO activity, but 56 patients (84%) had elevated XO activity (Chi^2 p<0.0001). Allantoin was elevated in CHF compared to reference control values (41.0±26.2 vs 13.4±1.6 µmol/L). In the double-blinded allopurinol treatment study, plasma XO activity was reduced in all 17 patients by 49% (from 4.35± 2.7± to 2.25±1.3, p<0.001). Allopurinol also reduced allantoin levels by 18% (from 25.7±4.1 to 21.1±1.0, p<0.02).
Conclusion: The activity of circulating plasma XO is elevated in patients with CHF. Treatment with allopurinol results in reduction of XO activity that is paralleled by lower allantoin indicating reduced oxygen radical load. Thus, a potentially new therapeutic option emerges to reduce oxygen radical load in CHF.

1184-82 **Chronic Monotherapy With Extended Release Metoprolol Succinate Attenuates mRNA Gene Expression for MMP2 and MMP9 in Dogs With Heart Failure**

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Background: Accumulation of collagen in the cardiac interstitium or "reactive interstitial fibrosis" (RIF) occurs in heart failure (HF) and contributes to LV dysfunction and remodeling. Matrix metalloproteinases (MMPs) are upregulated in HF and contribute to RIF. We previously showed that therapy with extended release metoprolol succinate (ER-MET) significantly reduces RIF in dogs with HF. In this study, we examined the effects of chronic therapy with ER-MET on gene expression of MMP2 and MMP9 (gelatinases) and on tissue inhibitors of MMPs (TIMPs) in LV of dogs with microembolization-induced HF.
Methods: Total RNA was isolated from LV tissue of 14 dogs with HF randomized to 3 months therapy with ER-MET (50 mg, once daily, n=7) or to no therapy at all (n=7) and from LV of 6 normal (NL) dogs. mRNA expression for MMP2 and 9 and TIMP1 and 2 was measured using reverse transcriptase polymerase chain reaction and bands quantified in densitometric units. **Results:** Results are shown in the table. There were no differences in expression of TIMP1 and 2 among the 3 study groups. Expression of MMP2 and 9 was increased in untreated-HF dogs compared to NL. ER-MET significantly reduced this increase in expression of MMP2 and 9. **Conclusions:** In dogs with HF, mRNA gene expression of TIMPs is unchanged while expression of MMP2 and 9 is increased. Therapy with ER-MET does not influence TIMPs but reduces expression of MMP2 and 9, a finding consistent with reduced RIF following chronic therapy with the ER-MET.

	NL	HF-Untreated	HF + ER-MET
TIMP1	2.33 ± 0.35	2.93 ± 0.46	1.90 ± 0.38
TIMP2	1.31 ± 0.04	1.39 ± 0.02	1.35 ± 0.06
MMP2	1.30 ± 0.18	2.04 ± 0.11*	1.39 ± 0..08^
MMP9	1.22 ± 0.14	2.50 ± 0.04*	1.15 ± 0.10^

*=P<0.05 vs. NL; ^=P<0.05 vs. HF-Untreated

1184-83 **Dietary Fish Oil Supplementation Improves Endothelial Function in Patients With Congestive Heart Failure**

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Background
Systemic vasoconstriction and reduced peripheral perfusion are hallmarks of congestive heart failure (CHF). Endothelial dysfunction is a frequent finding in CHF and is associated with reduced bioavailability of the vasodilator autocoid nitric oxide (NO). Omega-3-fatty acids (fish oils) have been shown to have beneficial effects on endothelial function and vascular responses in a number of vascular diseases which may be secondary to increased NO bioavailability. We conducted a study to establish whether addition of omega-3- fatty acids to background therapy in patients with CHF would improve endothelial dysfunction.
Methods
20 patients with grade II and III CHF (15 male) mean age 73 were recruited. Sodium nitroprusside (SNP) (6, 9, 12nmol/min) and acetylcholine (ACH) (120,180, 240nmol/min) were infused into the non-dominant brachial artery. Forearm blood flow (FABF) responses assessed by venous occlusion plethysmography. Patients received fish oil or olive oil drink for 6 weeks in a double blinded randomised cross over trial with assessment of FABF at baseline and after each treatment.
Results
See table
Conclusion
Dietary fish oil significantly improved endothelial function as assessed by FABF responses to ACH. There are several possible mechanisms by which fish oils could potentially improve endothelial function in CCF. Further studies are required to attempt to elucidate the mechanism for this improvement and to establish whether will be associated with improved outcomes.

Forearm Blood Flow responses to infusion of SNP and ACH (values are arbitary units) (*=p<0.01)

	SNP	ACH
Baseline 1	14.22 (10.93,17.51)	7.95 (4.81,11.80)
Fish oil	11.66 (8.17,15.15	11.27* (7.31,15.23)
Baseline 2	13.55 (10.74,16.36)	7.68 (4.95,10.41)
Olive oil	14.38 (11.67,17.09)	7.27 (4.66,9.88)

POSTER SESSION

1185 Cardiac Transplantation: Cellular Mechanisms and Rejection

Tuesday, April 01, 2003, Noon-2:00 p.m.
McCormick Place, Hall A
Presentation Hour: 1:00 p.m.-2:00 p.m.

1185-59 **Acute Rejection in Human Heart Transplantation: Identification and Characterization of Two Important Markers (MIP-1 β and VE-Cadherin)**

Ana L. S. Roussoulieres, Olivier Raisky, Lara Chalabreysse, George Dureau, Catherine Cerutti, Pascale Boissonnat, Laurent Sebbag, Jean-Paul Gare, Jean-François Obadia, Jean Ninet, Olivier Bastien, Françoise Thivolet-Bejui, John L. McGregor, Hôpital Cardiologique Louis Pradel, Lyon, France, INSERM, Lyon, France

Background: An extensive number of molecules are involved in acute rejection (AR) following heart transplantation. We have previously identified by DNA arrays, in a murine model of heterotopic heart transplantation, a number of genes implicated in allograft AR. The expression of 2 of these genes, MIP-1β and VE-Cadherin, was investigated in the present study as potential new markers of AR in cardiac tissue following human heart transplantation.
Methods: We have previously studied the expression profile of genes involved in AR